# How CBER Evaluates Post-Licensure Adverse Events

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CBER 101

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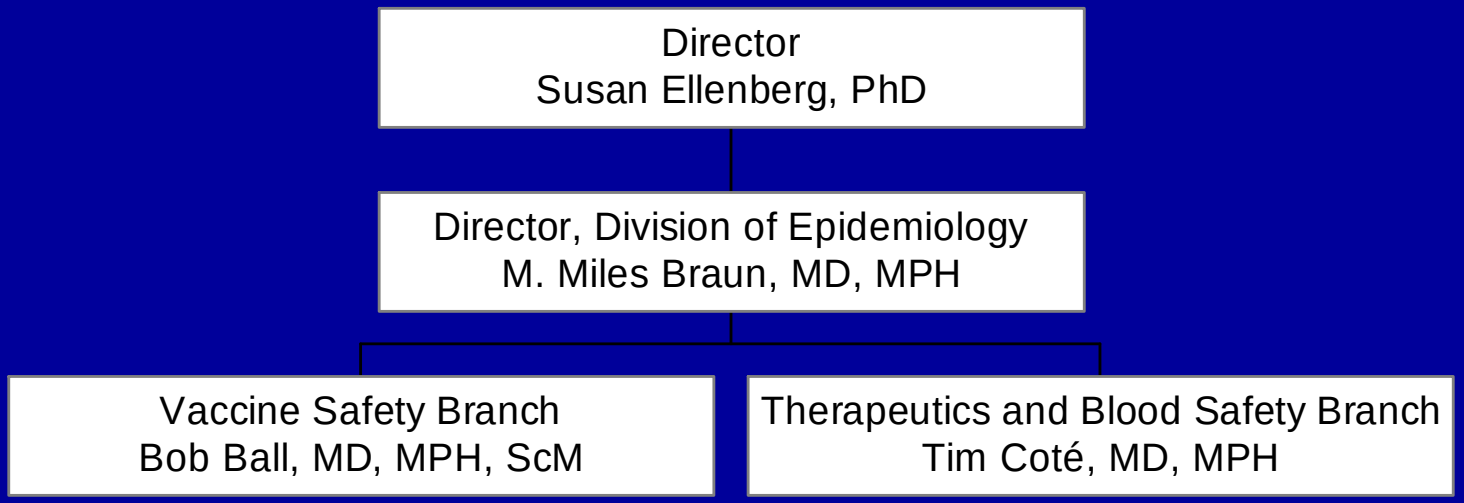
# Office of Biostatistics and Epidemiology
# Division of Epidemiology



# Post licensure Safety Surveillance

- (=Postmarketing surveillance)
- Why do it?
  - Prelicensure trials limitations
    - **size**
    - **duration**
    - **patient population: age, comorbidity, severity**
    - **exclusions**

# Mission, Division of Epidemiology

- To rapidly detect and rigorously research safety problems for licensed biological products, and to facilitate appropriate regulatory, risk communication and risk management actions to mitigate these problems. DE also provides consultation to meet epidemiologic needs of CBER

# Terminology

- Adverse Event vs. Reaction
- Incidence Rates vs. Reporting Rates
- Passive Surveillance = Spontaneous Reporting

# 21 CFR 600.80

- Proposed revision of rule (“The Tome”)
  - Published; comments being addressed by FDA
- For manufacturers
- 15-day Alert reports
  - “Serious”
  - Unexpected
- Periodic adverse experience reports
- 21CFR 600.81 Distribution Reports

# 21 CFR 600.80

- “Each periodic report shall contain: A narrative summary and analysis of the information in the report and an analysis of the 15-day reports…”

# Prescription Drug Users Fee Act (PDUFA 3) - October 1, 2002

- Guidance Development
  - Good risk assessment
  - Good risk management
  - Good pharmacovigilance

# Risk Management Program

- RMP is strategic safety program with
  - risk reduction goal(s) and
  - Intervention(s) in addition to PI
- Education, forms, processes, or other methods try to influence or control a product's:
  - Prescribing,
  - Dispensing
  - Use

# Risk Management Program Goals

- Reflect specific risk concerns
- Describe desired end result
- Include vision statement:

  **“No patient with condition A (e.g. pregnancy) should receive product B (e.g. teratogen).”**

# RMP Evaluation Process & Methods

- Evaluation to monitor effectiveness of risk management interventions:
  - Ensure positive benefit/risk balance
  - RMP improvement, modification
- Ideal:
  - Well defined, validated evaluation with measurements of health outcomes
  - ≥2 complementary evaluations of key goals

# Good Pharmacovigilance

- **Pharmacovigilance Practices**
- **Pharmacoepidemiologic Assessment**

# Pharmacovigilance Concept Paper Scope

- Important pharmacovigilance concepts
  - Safety signal identification
  - Pharmacoepidemiologic assessment and interpretation of safety signals
  - The development of pharmacovigilance plans
- Focus on risk assessment based on observational data
  - Case Reports, Case Series
  - Pharmacoepidemiologic Studies, Registries, Surveys

# PDUFA-3 Review Activities

- Risk management tools, plans or studies
- Proposed observational studies
- Phase 4 studies
- Post-licensure AE reporting requirements
- Product label
- Periodic Reports or PSURs
- Adverse event monitoring for products approved October 1, 2002 or later.

# AERS (MedWatch) and VAERS

- Brief, simple forms
- Direct reports
- Manufacturer Reports
- Computerized databases
- Contractor

# Passive Surveillance Systems: Weaknesses

- Missing or inaccurate data
- Underreporting
- Lack of controls
- Lack of accurate “denominator”
- Near inability to assess causality
- Detection of events with long latency

# VACCINE ADVERSE EVENT REPORTING SYSTEM

VAERS

24 Hour Toll-free information line 1-800-822-7967
P.O. Box 1100, Rockville, MD 20849-1100
PATIENT IDENTITY KEPT CONFIDENTIAL

***For CDC/FDA Use Only***

VAERS Number _____

Date Received _____

Patient Name:

Last First M.I.

Address

City State Zip

Telephone no. (_____)_____

Vaccine administered by (Name):

Responsible Physician _____

Facility Name/Address

City State Zip

Telephone no. (_____)_____

Form completed by (Name):

Relation to Patient ☐ Vaccine Provider ☐ Patient/Parent ☐ Manufacturer ☐ Other

Address *(if different from patient or provider)*

City State Zip

Telephone no. (_____)_____

| 1. State | 2. County where administered | 3. Date of birth mm / dd / yy | 4. Patient age | 5. Sex ☐ M ☐ F | 6. Date form completed mm / dd / yy |
|---|---|---|---|---|---|
| | | | | | |

**7.** Describe adverse event(s) (symptoms, signs, time course) and treatment, if any

**8.** Check all appropriate:

- ☐ Patient died (date ___/___/___ mm dd yy)
- ☐ Life threatening illness
- ☐ Required emergency room/doctor visit
- ☐ Required hospitalization (_____days)
- ☐ Resulted in prolongation of hospitalization
- ☐ Resulted in permanent disability
- ☐ None of the above

9. Patient recovered ☐ YES ☐ NO ☐ UNKNOWN

12. Relevant diagnostic tests/laboratory data

**10.** Date of vaccination mm / dd / yy

Time _____ AM PM

**11.** Adverse event onset mm / dd / yy

Time _____ AM PM

**13.** Enter all vaccines given on date listed in no. 10

| | Vaccine (type) | Manufacturer | Lot number | Route/Site | No. Previous doses |
|---|---|---|---|---|---|
| a. | | | | | |
| b. | | | | | |
| c. | | | | | |
| d. | | | | | |

14. Any other vaccinations within 4 weeks prior to the date listed in no. 10

| | Vaccine (type) | Manufacturer | Lot number | Route/Site | No. Previous doses | Date given |
|---|---|---|---|---|---|---|
| a. | | | | | | |
| b. | | | | | | |

15. Vaccinated at:
☐ Private doctor's office/hospital ☐ Military clinic/hospital
☐ Public health clinic/hospital ☐ Other/unknown

16. Vaccine purchased with:
☐ Private funds ☐ Military funds
☐ Public funds ☐ Other /unknown

17. Other medications

18. Illness at time of vaccination (specify)

19. Pre-existing physician-diagnosed allergies, birth defects, medical conditions (specify)

20. Have you reported this adverse event previously? ☐ No ☐ To health department ☐ To doctor ☐ To manufacturer

***Only for children 5 and under***

22. Birth weight _____ lb. _____ oz.

23. No. of brothers and sisters

21. Adverse event following prior vaccination (check all applicable, specify)

***Only for reports submitted by manufacturer/immunization project***

# MedWatch 3500A Mandatory Reporting Form

Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

**MEDWATCH**
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr report #
UF/Dist report #
FDA Use Only

PLEASE TYPE OR USE BLACK INK

## A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex: ☐ female ☐ male
4. Weight: _____ lbs or _____ kgs

## B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death _____ (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: _____
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

## C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1
   #2
2. Dose, frequency & route used
   #1
   #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate)
   #1
   #2
4. Diagnosis for use (indication)
   #1
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1
   #2
7. Exp. date (if known)
   #1
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☐ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # – for product problems only (if known)
   – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

## D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other: _____
5. Expiration date (mo/day/yr)
6. model # _____
   catalog # _____
   serial # _____
   lot # _____
   other # _____
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA)
   ☐ yes ☐ no ☐ returned to manufacturer on _____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

## E. Initial reporter

1. Name & address
   phone #
2. Health professional? ☐ yes ☐ no
3. Occupation
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☐ unk

FDA Form 3500A

**Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.**

# Knee-Jerk Dismissal of Signal from Spontaneous Reports

- Poor quality, not “hard data”
- Not shown in clinical trials
- Adverse event not biologically plausible
- Just a background event
- Reporting rate < Background incidence rate
- Don’t impugn a great product!

# Passive Surveillance Systems: Strengths

- Detect rare adverse events
- Timely availability of data
- National (and International) Coverage
- Lot-specific safety assessment
- Hypothesis generation

## AERS

- CDER & CBER
- Non-vaccine biologics
- Medwatch Form
- Mostly serious reports
- ~3K CBER rpts/year*
- Adults predominate

## VAERS

- CDC & CBER
- Vaccines
- VAERS Form
- Mostly non-serious
- ~15K reports/year
- Many infants, children

* May increase substantially if proposed rules become final

# National Childhood Vaccine Injury Act of 1986, as amended

- Addresses vaccine liability concerns:
  - limited to universally recommended childhood vaccines
- Mandated U.S. vaccine safety infrastructure
  - National Vaccine Program Office (NVPO)
  - National Vaccine Injury Compensation Program (NVICP): Vaccine Excise Tax + Vaccine Injury Table
  - Vaccine Information Statements (VIS)
  - Institute of Medicine (IOM) review committee
  - *Vaccine Adverse Events Reporting System (VAERS)*

# First Line Screening of Serious VAERS Reports

- Contractor data entry
- Contractor follow-up nurses
- FDA: Medical Officer review
- FDA “lot” meeting

# Definition of Signal, WHO

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously."

- Edwards & Biriell, Drug Safety 1994;10:93

# Definitions of Signal from Waller & Lee, 1999

- Alert from any source that a drug may be associated with a previously unrecognized hazard…
- In practice: Something, that if found to be drug-related, would be considered clinically important and might impact on patient management…
- A series of cases of similar suspected adverse reactions...

# Transmitters and Receivers of Signals:

- Consumers
- Activists
- Clinicians
- Scientists
- Pharmacovigilance staff
- Pharmaceutical manufacturers
- Politicians
- Communications Media
- Any person or group

# Signal Amplification Examples

- Individual adverse event report review
- PSURs, Periodic Reports
- Scientific publications
- “Data mining”
- Information requests
- Publicity

# A signal may seem to be “in the eye of the beholder”

- Whose assessment is paramount?
- What criteria are used to assess the signal?
- Which signal is more important?
- Is action needed?

# Fundamental Problem in Assessing Spontaneous Reports

- VAERS ~10-15K reports / year
- AERS ~3K reports /year (CBER)*
- How can a sensitive system to detect potential product problems not be overloaded and overwhelmed by information to which we have to respond?

* May increase substantially if proposed rules become final

# Filtration of Massive Number of Adverse Event Reports:

- Seriousness
- Number of  reports
- Newness: in label?  in literature?
- reporting rates vs. background rates
- “Data Mining”
- Clinical Trials, other studies

# How many reports to generate an hypothesis?

- Wide range of possibilities
- As few as one (eg, positive rechallenge)
- 3+ for relatively rare events
- Relates to “background rate of adverse event of interest

# The Value of Case Series: MMWR, June 5, 1981

- 5 cases PCP pneumonia, 2 died
- “Homosexuals”
- Previously healthy
- Editorial
  - “cellular immune dysfunction related to a common exposure”
  - “disease acquired through sexual contact”

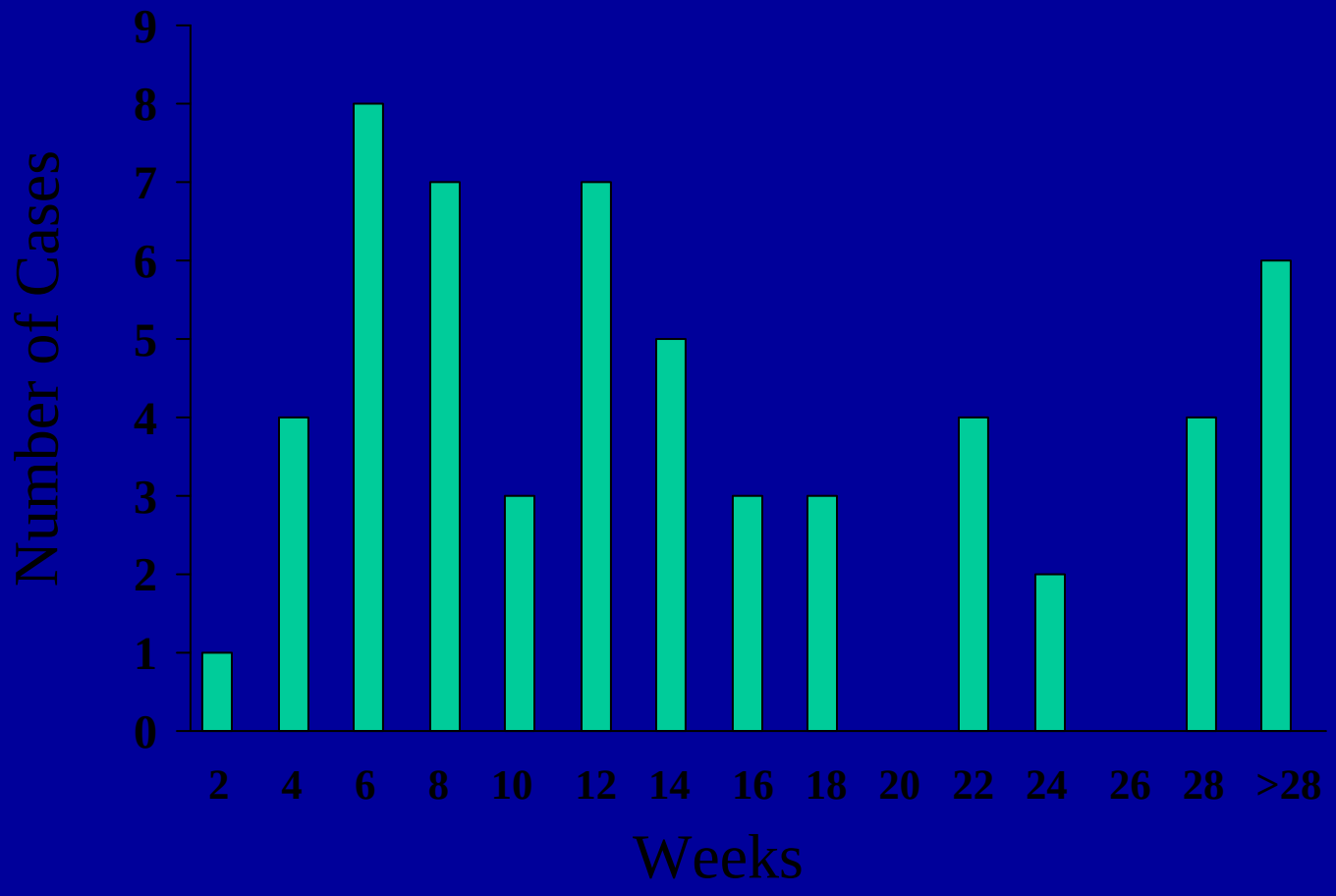
# Infliximab and Tuberculosis
## *Background*

- Licensed by FDA 1998
- Monoclonal Antibody
- Binds Tumor Necrosis Factor alfa (TNFa)
- TNF alfa is inflammatory cytokine
- Indications: Rheumatoid arthritis
  Crohn's Disease
- Infusions at 0,2,6 weeks then 8 wk intervals

# Infliximab

- TNF alfa role in fighting infection
- Early post-licensure period: occasional reports to FDA of serious infections
- Tuberculosis, histoplasmosis, coccidiodomycosis, listeriosis

# Time From Initiation of Infliximab Therapy to Diagnosis of Tuberculosis




N Eng J Med. 2001;345:1098-104.

# Evidence for Causal Association

- High reporting rates compared to "background" incidence rates
- Temporal association
- Mouse data

# Public Health Response: Infliximab & Tuberculosis

- Presentations at medical conferences
- Publication in NEJM
- Dear Healthcare Provider letter
- Boxed warning in product package insert
- FDA Advisory Committee Meetings
- Interaction with CDC TB Division
- Encouraged company educational program for healthcare providers→**TB screening of patients before administering infliximab**

# Analysis of Surveillance Data: Signal Detection--Qualitative

- Unexpected patterns in case reports
  - Clinical
  - Demographic
  - Time to onset
- “Positive rechallenge” reports
- Signals almost always require confirmation in a controlled study

# Analysis of Surveillance Data: Signal Detection--Quantitative

- Reporting rates vs. background rates
- “Data mining”
- Quantitative methods susceptible to biases and reporting artifact
- Medical knowledge and independent confirmation necessary, as with qualitative approaches

# Causality Determination is Part of Signal Filtration

- Biologic plausibility
- Temporal association
  - Time to onset
  - Rechallenge, Dechallenge
- Dose-response
- Strength of association
- Specificity
- Analogy
- Consistency of data
- Alternative explanations

# Rotavirus Vaccine-Intussusception

- Clinical Trials Signal
- Wild type RV & intussusception study
- FDA - licensure
- CDC - recommendations for use
- Post-marketing Surveillance (VAERS)
- Background rates
- Population-based incidence rates
- Withdrawal

# Important Characteristics RV- Intussusception

- Age
- Dose
- Severity
- Acute onset
- Interval from vaccination to intussusception

# Elusive Background Rates

- Say we have X occurrences of event Y,
- What is the expected number of events?
- Medical Literature, sometimes has them
  - Generalizability?
  - Subgroups
- Other sources
- For X, how high is high?
- Example: intussusception and RV vaccine

# “Data Mining”

- Uses only adverse event reports
- Versions or “brands”.  Examples:
  - Empirical Bayesian Geometric Mean (EBGM)
  - Proportial Reporting Ratios (PRR)
- Ranks product-adverse event associations
- Implementation in progress:
  - FDA AERS
  - FDA & CDC VAERS

# Signal's Importance to us Depends on:

- Health impact
  - Severity
  - Numbers of reports
- Causality assessment (preliminary)
- Effective Intervention possible?

# Lingering Vaccine-AE Signals

- Gulf War Syndrome
- Rheumatologic condition
  - Arthritis
- Neuro-psychiatric condition
  - Autism
  - Cognitive dysfunction

# Hard-to-Dismiss Signals

- Chronic disease
- Unknown cause
- Insidious onset
- Exposure-onset interval unclear
- “Subjective” complaints
- Ill-defined disease
- REAL DRUG REACTIONS!

# Adverse Event Responses

- Evaluation of Signals
- Change to Package Insert (“Label”)
- “Dear Doctor Letter”
- Professional Mtg Presentations/Abstracts
- Peer-reviewed Publications
- Risk Management Program
- Product Withdrawal

# Previously Reported Risks/Medical Errors

- Group A Strep infection of transplanted tissue (MMWR 2003; 52:1173-1176)
- Pure red cell aplasia associated with erythropoeitin administration (N Engl J Med. 2002; 346:1584-6)
- Anti-TNF therapy and increased risk of TB (N Eng J Med. 2001; 345:1098-104)
- Intravascular hemolysis after WinRho for ITP (Blood, 2000; 95:2523-2529)
- Postlicensure safety surveillance for varicella vaccine. (*JAMA* 2000;284:1271-9.)
- Inappropriate dilution of serum albumin with sterile water (MMWR, 1999; 48:157-162)